REMARKS

Applicant respectfully requests reconsideration.

Claims 1, 2, 5-7, 9, 11-17, 19-34, 68, 91, 125, 126 and 128-130 were previously pending in this application.

Claims 16, 22 and 23 are cancelled without prejudice or disclaimer. Claims 1, 11-15, 17, 68, 91, 125, 126 and 130 are amended. Support for these amendments can be found in the claims as originally filed and in the specification at least on page 3 lines 30-31, page 4 lines 5-6, page 25 lines 1 and 16-21, and page 26 lines 16-19 and 22-30. Applicant reserves the right to pursue the subject matter of the claims as originally filed and/or as previously pending in one or more continuing applications.

No new matter has been added.

Claims 1, 2, 5-7, 9, 11-15, 17, 19-21, 24-34, 68, 91, 125, 126 and 128-130 are pending for examination.

Claim Objections

Claims 11 and 12 are objected to for the recitation of "enzyme". The claims have been amended to recite "nucleic acid binding enzyme" for consistency with claim 1 from which each depends, as suggested by the Examiner. Reconsideration and withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. §102

Claims 1, 2, 5-7, 11, 13-16, 24-26, 31, 91, 126, 128 and 129 are rejected under 35 U.S.C. §102(b) as being anticipated by Cheng et al. (Biochem. Biophys. Res. Commun. 1991, 174(2):785-789).

The Examiner maintains that Cheng et al. anticipates the rejected claims because the rejected claims recite no particular order of steps and thus "do not exclude a method wherein the "providing" step and the "contacting" step occur simultaneously. Applicant traverses.

Applicant has addressed the teachings of Cheng et al. in previous responses. In particular, Applicant has introduced the "first step", "second step, and optionally "third step" limitations into

claims 1, 91, 126 and 129 in order to convey an order. One of ordinary skill in the art would readily understand that such recitations imply that the "first" step of providing occurs prior to, and not simultaneously with, the "second" step of contacting. The plain meanings of "first", "second" and "third" convey this.

The Examiner cites MPEP 2111.01(II) to support the rejection. However, that section of the MPEP supports Applicant's, rather than the Examiner's, position. In particular, it cites from *Altiris Inc. v. Symantec Corp.*, 318 F.3d 1363, 1371, 65 USPQ2d 1865, 1869-70 (Fed. Cir. 2003) which held that "Although the specification discussed only a single embodiment, the court held that it was *improper to read a specific order of steps into method claims where, as a matter of logic or grammar, the language of the method claims did not impose a specific order on the performance of the method steps*, and the specification did not directly or implicitly require a particular order." (emphasis added) The rejected claims are an example of where, as a matter of logic and grammar, the language of the method claims impose a specific order on the performance of the method steps. First, as argued above, the plain meaning of first, second and third denotes a specific order. Second, changing the order of the steps would be non-sensical at least because the conjugate must first exist prior to its contact with the nucleic acid polymer. To be sure, under the Examiner's rationale, the claim could also be read as first contacting a nucleic acid with *the* conjugate and then providing *a* conjugate. As a matter of logic, grammar, and proper antecedent basis, it is wholly inappropriate to construe the claim in this manner.

Finally, the Examiner has already acknowledged that the method steps have a particular order. For example, in the Advisory Action dated November 17, 2008, the Examiner states "In the proposed amendment (dated November 4, 2008 and including the first, second and third step limitations), claims 1, 91, 126, and 129 have been amended to recite that *the method steps occur in a particular order*." (emphasis added) The Examiner's current position is inconsistent with her previous position and, more importantly, it is not supported by plain language and meaning of the claims.

One of ordinary skill in the art would readily understand, based on the plain language and meaning of the claims, that a conjugate must exist prior to its contact with a nucleic acid polymer, and consequently that the providing and contacting steps cannot occur simultaneously. In the

method of Cheng et al. an rA_{12-18} strand is *first* hybridized to a dT_{10} strand and *then* the resulting duplex is contacted with the reverse transcriptase (RT) in the crosslinking reaction. In this method, a covalent conjugate comprising RT and one of the oligo strands is *not* first formed. The Examiner acknowledges as much when she concludes that Cheng et al. provides and contacts the conjugate simultaneously.

For at least the foregoing reasons, Cheng et al. does not anticipate the rejected claims. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 125 is rejected under 35 U.S.C. §102(b) as being anticipated by Fisher et al. (WO 98/19168 A1) as evidenced by Chaudhry et al. (Nucleic Acids Research, 1995, 23(19):3805-3809).

The Examiner maintains that Fisher et al. teaches a "nucleic acid binding enzyme (in the form of nuclease P1) that inherently binds non-specifically to the nucleic acid polymer at least transiently, since it is conjugated to a short oligonucleotide that specifically binds to the nucleic acid polymer." Applicant traverses.

Fisher et al. teaches a covalent conjugate comprising nuclease P1 and a nucleic acid that can be hybridized to target nucleic acids immobilized on a solid support. According to Fisher et al. "the nuclease P1-oligonucleotide conjugate binds to another site on the target nucleic acid, producing an immobilized complex labelled with nuclease P1. Following a number of washing steps nuclease P1 which has become immobilized in this way can be detected ...". The oligonucleotide in the conjugate represents a "specific binding member". One of ordinary skill in the art would clearly understand, based on the teachings in Fisher et al., that the oligonucleotide binds to the target nucleic acid in a sequence-specific manner (i.e., via complementary hybridization) and nuclease P1 is the label that is detected in order to ascertain binding of the oligonucleotide to the target. One of ordinary skill would also appreciate that nuclease P1 does not bind to the target directly and rather that its binding may be considered "indirect" since it occurs via the sequence-specific binding of the oligonucleotide. Accordingly, the indirect binding of nuclease P1 may only be characterized as sequence-specific since it interacts with the target nucleic acid only by virtue of its covalent link to the oligonucleotide which binds to the target in a sequence-specific manner. The Examiner's conclusion that nuclease P1 inherently binds non-specifically to the target in supported and appears

to confuse indirect binding with non-specific binding. Nuclease P1 binds indirectly to the target but such binding is not non-specific. If this were the case, then the binding of the oligonucleotide to the target would have to be non-specific, and this would clearly undermine the purpose of the sandwich assay of the Fisher et al.

Moreover, there is no teaching in Fisher et al. that nuclease P1 binds directly to the target nucleic acid. Fisher et al. requires that nuclease P1 bind to its substrate in order to function as a label, and such substrate is not the target nucleic acid.

Fisher et al. does not teach non-specific binding of a nucleic acid binding agent to a target nucleic acid at least because Fisher et al. does not teach nuclease P1 binding that is independent of oligonucleotide binding to the target. For at least these reasons, Fisher et al. does not anticipate claim 125. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 2, 5, 6, 9, 11-16, 24-27, 31, 91, 125, 126, 128 and 130 are rejected under 35 U.S.C. §102(b) and §102(e) as being anticipated by JP 2001/190282A (Taira et al. I) and US 20030199471 A1 (Taira et al. II), respectively. The Examiner has indicated that US 20030199471 A1 is the English language equivalent of JP 2001/190282A. Accordingly, the rejections in view of these references are identical. Applicant's response is framed in the context of US 20030199471 A1 but it is to be understood that it applies equally to JP 2001/190282A. Applicant traverses in part.

Claims 1, 13, 14, 15, 125, 126 and 130 are amended to recite that the nucleic acid polymer is fluorescently-labeled and that either or both the nucleic acid tag molecule and nucleic acid binding enzyme (or agent) is fluorescently labeled. Support for these amendments can be found in the originally filed claims (see, for example, claims 13-17, 22 and 23) and in the specification at least on page 3 lines 30-31, page 4 lines 5-6, page 25 lines 1 and 16-21, and page 26 lines 16-19 and 24-30. Claim 91 is amended to recite a third step of determining position of one or more conjugates when bound to the nucleic acid molecule. Support for this amendment can be found in the specification at least on page 26 lines 22-24.

Taira et al. II does not teach all the limitations of the claims as now amended.

With respect to claims 1, 125, 126 and 130 and the rejected claims that depend therefrom, Taira et al. II does not teach fluorescently-labeling a nucleic acid polymer and at the same time fluorescently-labeling one or both of the nucleic acid tag molecule and the nucleic acid binding enzyme (or agent). Instead Taira et al. II provides instances where only the target is labeled (see paragraphs 156, 157, 206 and 207, where this is done to evaluate cleavage of the target by a ribozyme), where only the helicase is labeled (see paragraphs 162 and 163, where this is done to evaluate binding of ribozyme to the helicase), and where both the ribozyme and helicase, but not the target, are labeled (see paragraphs 164 and 165, where this is done to evaluate binding of ribozyme to the helicase). In no instance did Taira et al. II report using labeled ribozyme or labeled helicase, together with a labeled target nucleic acid. Moreover, in no instance did Taira et al. II fluorescently label any of these components.

With respect to claim 91, Taira et al. II does not teach determining position(s) of one or more conjugates while bound to a nucleic acid molecule. Taira et al. II does not analyze target nucleic acids while such nucleic acids are bound to ribozyme or ribozyme/helicase complexes. Rather Taira et al. analyzes the downstream effects of such binding by way of target cleavage, target unwinding, and/or changes in target levels. Taira et al. does so because its interest is in modulating the activity and function of the target nucleic acids. In none of these downstream readouts is the ribozyme or ribozyme/helicase complex still bound to the target.

For at least these reasons, Taira et al. I and II do not provide all the limitations of the rejected claims, as now amended, and therefore the references do not anticipate such claims. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103

Claims 17, 22, 23 and 28-30 are rejected under 35 U.S.C. §103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1) in view of Daskis et al. (WO 2001/46467 A2) and further in view of Thompson et al. (US 6,348,317 B1).

Applicant traverses in part. Claim 1, from which the rejected claims depend, has been amended. These amendments and their support are described above. Claims 22 and 23 are cancelled. The rejected claims include the limitation that the nucleic acid polymer and one or both

of the nucleic acid tag molecule and the nucleic acid binding enzyme are fluorescently-labeled. Taira et al. II does not provide these limitations.

The Examiner considers that it would have been obvious to combine Taira et al. II with Daskis et al. because "an ordinary artisan would have been motivated to label the nucleic acid tag molecule (i.e., the ribozyme) and the mRNA target molecule of Taira using the backbone-specific fluorescent intercalating agents taught by Daskis ... (and that) ... the ordinary artisan would have been motivated to do so in order to obtain a rapid, sensitive, environmentally friendly, safe, and homogeneous method for analyzing the binding between the ribozyme-helicase conjugates of Taira and their mRNA targets." Applicant disagrees. Taira et al. II provides no motivation nor any reasonable rationale for labeling (let alone fluorescently-labeling) its mRNA target while at the same time fluorescently-labeling one or both of its ribozyme and helicase. Taira et al. II studies the downstream effects of ribozyme and/or ribozyme/helicase on nucleic acid targets. These downstream effects include cleavage of the target, unwinding of the target, and changes in the expression levels of the target. Such downstream effects do not require labeling (let alone fluorescent-labeling) of the target and at least one of the ribozyme or the helicase. One of ordinary skill in the art, upon reading Taira et al. in its entirety, would not be motivated to label ribozymes and targets at the same time, as indicated by the Examiner, because the interaction between the ribozyme-helicase conjugates and mRNA targets are analyzed by Taira et al. II through downstream readouts such as target cleavage, target unwinding, and modulation of target expression levels, as clearly and repeatedly taught by Taira et al. II.

For at least this reason, the combination does not render obvious the rejected claims. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 19, 20, 22, 23, 33, 34 and 68 are rejected under 35 U.S.C. §103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1) in view of Tegenfeldt et al. (WO 00/09757).

Applicant traverses in part. Claim 1, from which claims 19, 20, 22, 23, 33, 34 depend, has been amended. Claim 68 has been similarly amended. These amendments and their support are described above. Claims 22 and 23 are cancelled. The rejected claims include the limitation that the nucleic acid polymer and one or both of the nucleic acid tag molecule and the nucleic acid

binding enzyme are fluorescently-labeled. Taira et al. II does not provide these limitations. Taira et al. II does not label (let alone fluorescently label) its target nucleic acid and one or both of its ribozyme and its helicase. Tegenfeldt et al. does not provide such teachings either.

The Examiner considers that it would have been obvious to "use the detection system of Tegenfeldt et al. to analyze the hybridization patterns produced by the method of Taira et al." Applicant disagrees. Taira et al. II does not study hybridization patterns. Instead, Taira et al. II analyzes the downstream effects of ribozyme and helicases on target nucleic acids. Such downstream effects include target cleavage, target unwinding, and modulation of target expression levels. In no instance does Taira et al. directly analyze the interaction between ribozyme/helicase complexes and target nucleic acids. Accordingly, the ordinary artisan would not have been motivated to use the detection system of Tegenfeldt et al. instead of the assays used by Taira et al. given the nature of the readouts obtained by Taira et al. II.

For at least these reasons, the combination of references does not render obvious the rejected claims. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 21-23 and 32 are rejected under 35 U.S.C. §103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1) in view of Bertrand et al. (RNA, 1997, 3:75-88).

Applicant traverses in part. Claim 1, from which the rejected claims depend, has been amended. These amendments and their support are described above. Claims 22 and 23 are cancelled. The rejected claims therefore now include the limitation that the nucleic acid polymer and one or both of the nucleic acid tag molecule and the nucleic acid binding enzyme are fluorescently-labeled. Taira et al. II does not provide these limitations. Taira et al. II does not label (let alone fluorescently label) its target nucleic acid and one or both of its ribozyme and its helicase. Bertrand et al. does not provide such teachings either.

The Examiner concludes that one of ordinary skill in the art would have been motivated "to monitor intracellular localization of the helicase-ribozyme conjugates of Taira using FISH." The Examiner states that the Northern analysis used by Taira et al. II to study such localization could equivalently be studied using the FISH method of Bertrand et al. The passages cited by the Examiner however relate to experiments intended to determine whether and where ribozymes

and/or ribozyme/helicase complexes are present in cells. Such analyses do not require or even involve target nucleic acids. Rather these experiments simply determine the presence and location of ribozymes or ribozyme/helicase complexes in cells independently of targets. Therefore, the combination suggested by the Examiner, even if possible, would not render obvious the rejected claims because it does not yield all the limitations of those claims.

For at least these reasons, the combination of references does not render obvious the rejected claims. Reconsideration and withdrawal of this rejection is respectfully requested.

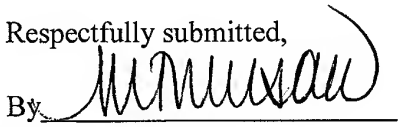
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. C0989.70054US00 from which the undersigned is authorized to draw.

Dated: September 4, 2009

Respectfully submitted,

By 

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